PHARMACOLOGY

Drugs & the Liver

Skye McKennon, PharmD. BCPS, ACSM-GEI

WASHINGTON STATE UNIVERSITY
Elson S. Floyd College of Medicine

DISCLOSURE

None

Use Statement

OBJECTIVES

1. Describe adverse effects of and contraindications to acetaminophen
2. Describe the mechanism of acetaminophen-induced liver damage
3. Summarize the treatment of acetaminophen overdose
4. Name substrates, inducers, and inhibitors of common cytochrome P450 3A4 drug interactions
5. Describe clinical manifestations of cytochrome P450 3A4 drug interactions

AGENDA

- Acetaminophen
- Acetaminophen-Induced Liver Damage & Treatment
- Drug Interactions
- Questions

THE CASE OF UR

UR is a 25-year-old male medical student that wakes up the morning after an anatomy pin test with a fever. UR decides to take an over-the counter medication. UR has no other medical conditions, takes only a multivitamin daily, and has an allergy to ibuprofen (hives). Which over-the-counter medications would be most appropriate for UR to use for their fever? Defend your answer.

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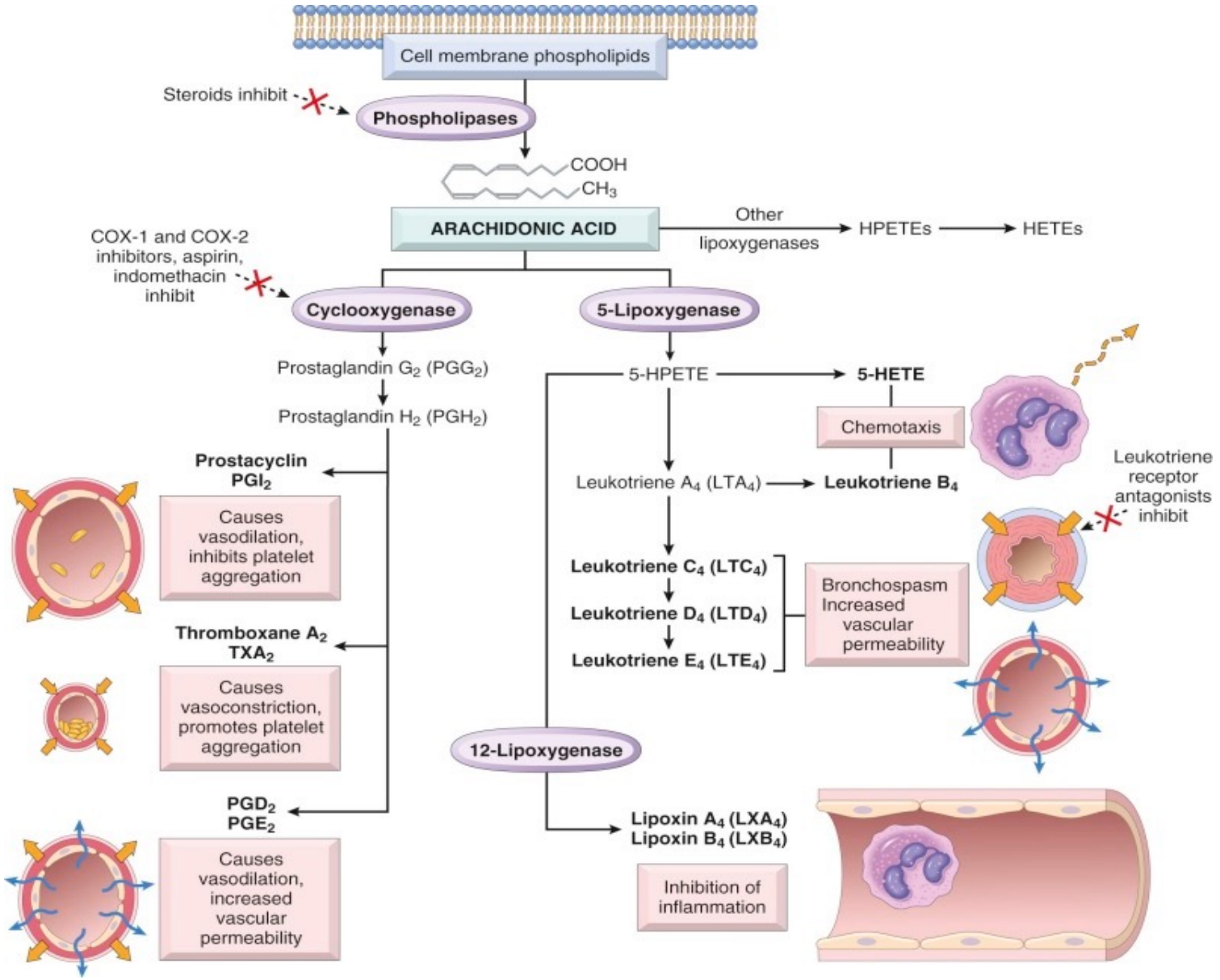
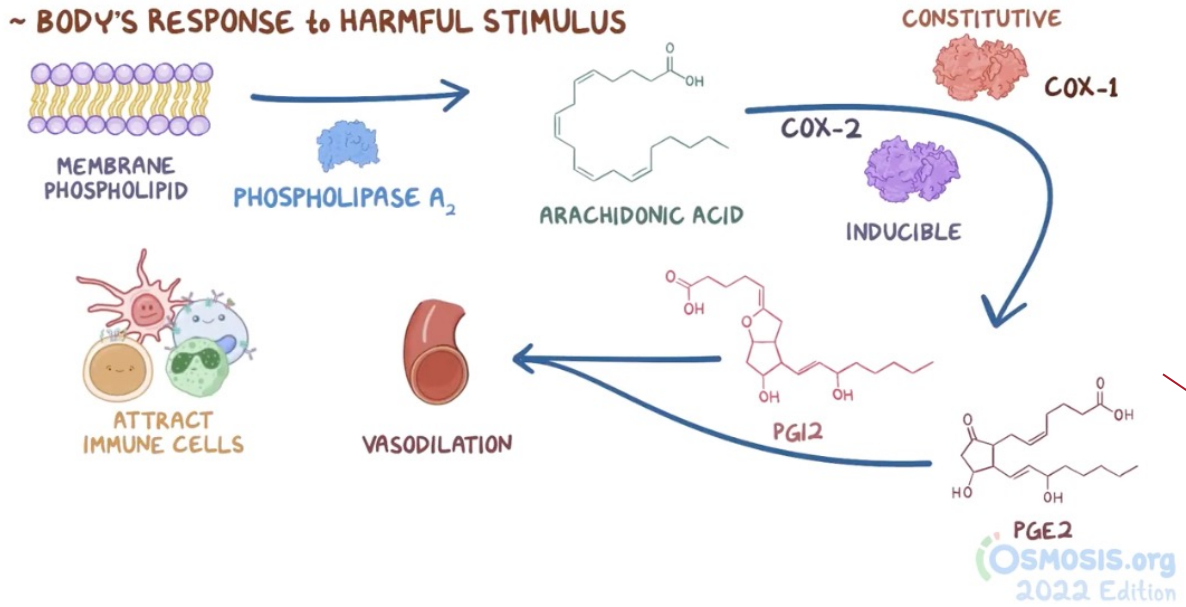
ACETAMINOPHEN

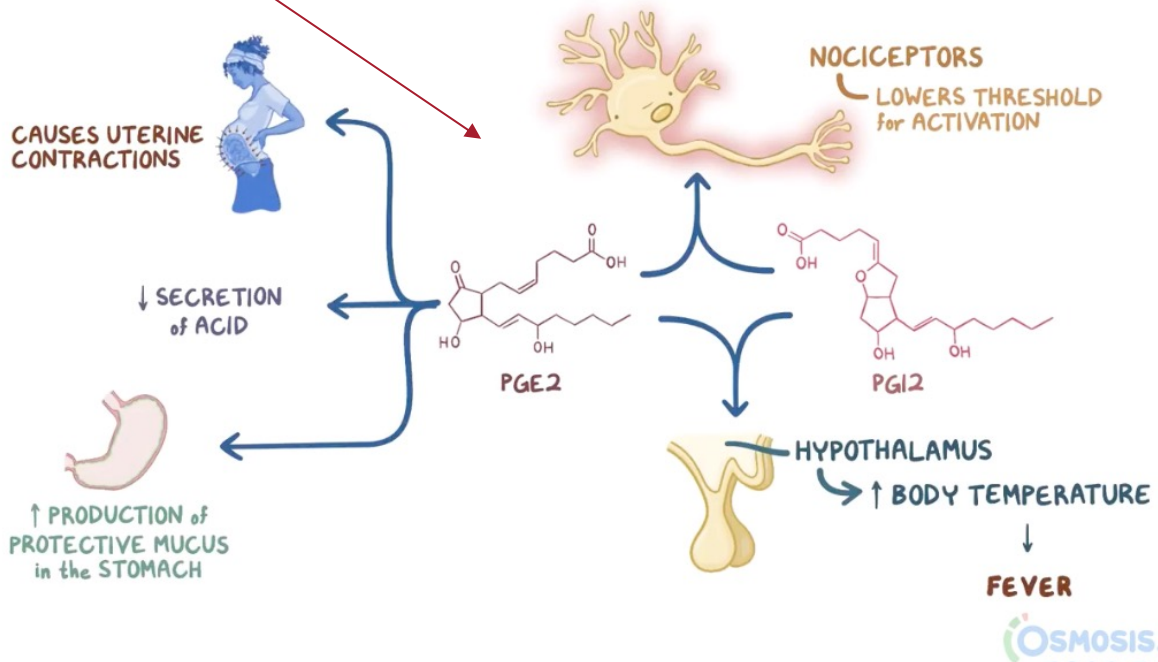
ARACHIDONIC ACID PATHWAY (INFLAMMATORY CASCADE)



INFLAMMATION

~ BODY'S RESPONSE to HARMFUL STIMULUS





ACETAMINOPHEN MECHANISM OF ACTION

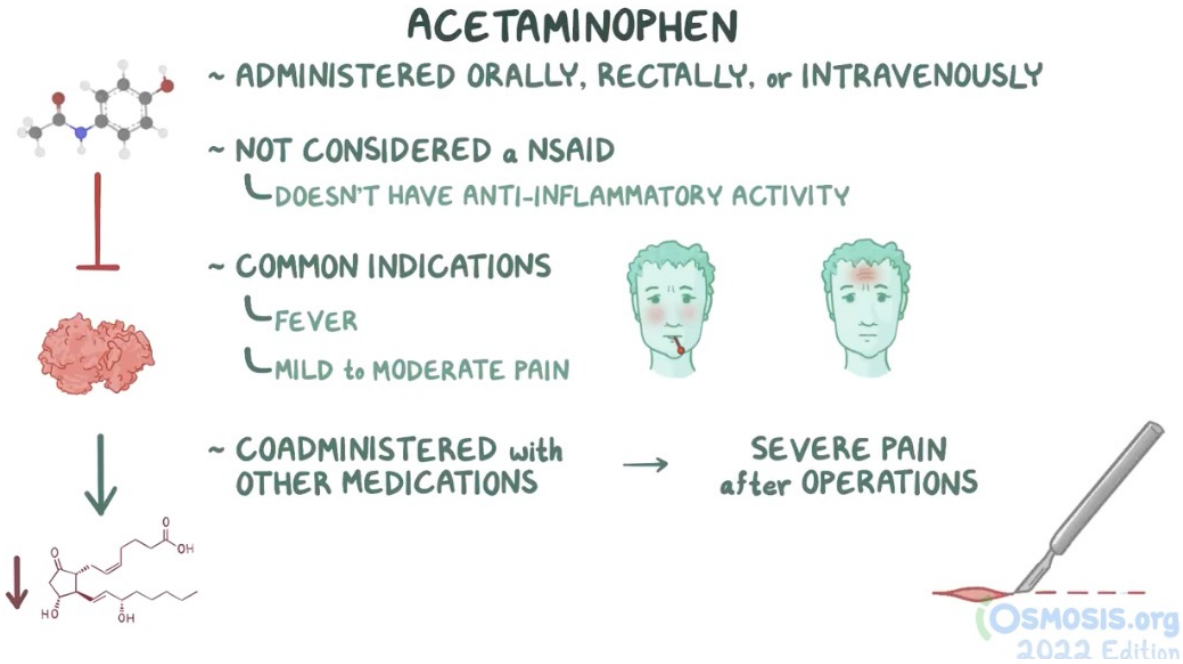
N-Acetyl-P-Aminophenol or APAP

Weak nonspecific COX inhibitor

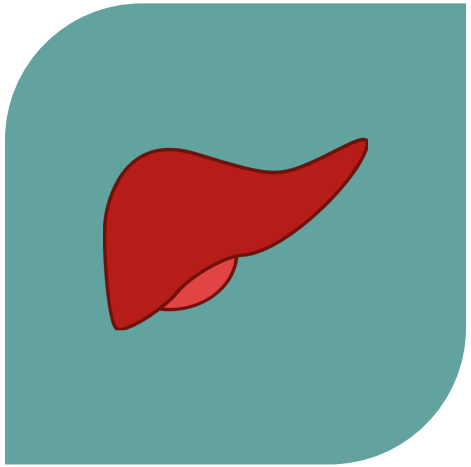
- Thought to work centrally (not peripherally)
- Decreased production of prostaglandins, prostacyclin

Lack of/low anti-inflammatory effect

Lack of antiplatelet effects



MAIN ADVERSE EFFECT OF ACETAMINOPHEN



HEPATIC

(HEPATOXICITY)

ACETAMINOPHEN

Drugs	Contraindications & Cautions	Adverse Effects	Selected Interactions
Acetaminophen (Tylenol)	**Severe hepatic impairment or severe active liver disease** G6PD deficiency Limit dose for all sources to < 4 g/day	**Acute hepatotoxicity** Dizziness Anemia Increased liver enzymes Rash	May increase the hepatotoxicity of other hepatotoxic drugs Alcohol Phenytoin/fosphenytoin may decrease APAP levels, but increase NAPQI levels

CLINICAL USE & ADME

Pain

Fever

Combined with other medications (eg, opioids) for severe pain

Generally well absorbed orally, rectally

- Available intravenously

Metabolism

- Phase I: CYP2E1 to toxic metabolite
- Phase II: Glucuronidation, sulfation

Elimination

- Renally (<5% unchanged in urine; 60–80% as glucuronide metabolites)

THE CASE OF UR

UR decides to take acetaminophen for their fever. They purchase acetaminophen 325 mg tablets. UR takes two at 8:30 am. How many more tablets can UR use in the next 24 hours? Why?

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ACETAMINOPHEN-INDUCED LIVER DAMAGE & TREATMENT

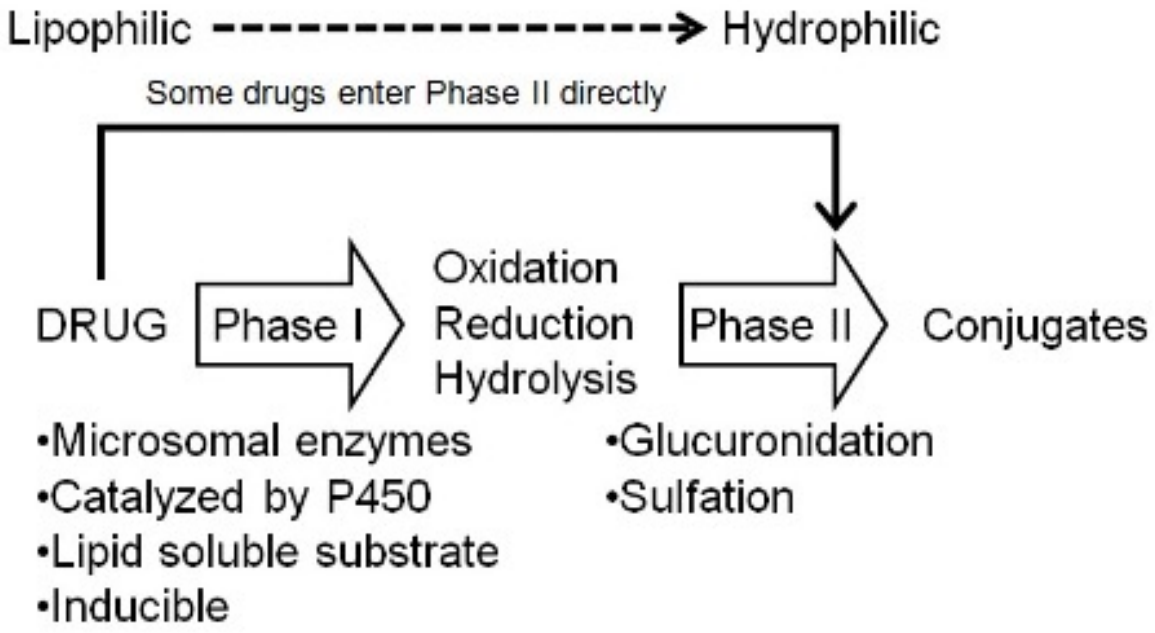
METABOLISM

Metabolism is the process by which **enzymes** in the body catalyze reactions that **change the chemical structure of a drug**

Principle site of metabolism is the liver

Drugs may be metabolized via phase I and/or phase II

- Mediated by different families of enzymes



METABOLISM: PHASE I REACTIONS

Lead to exposure/introduction of functional groups

- Render the drug more likely to undergo metabolism by a phase II enzyme that will increase polarity
- Minimal impact on water solubility

Most phase I reactions catalyzed by cytochrome P450 (CYPs or P450s) enzyme superfamily

- CYPs in families 1, 2, and 3 mediate Phase I metabolism of ~80% of drugs
- A single compound may be metabolized by multiple different CYPs

METABOLISM: PHASE II REACTIONS

Synthetic (conjugation) reactions that result in metabolite with increased molecular mass and substantially increased hydrophilicity

- Glucuronidation, sulfation, methylation, N-acetylation, glutathionylation

Catalyzed by

- Transferases (eg, glutathione-S-transferase, UDP-glucuronosyltransferases)

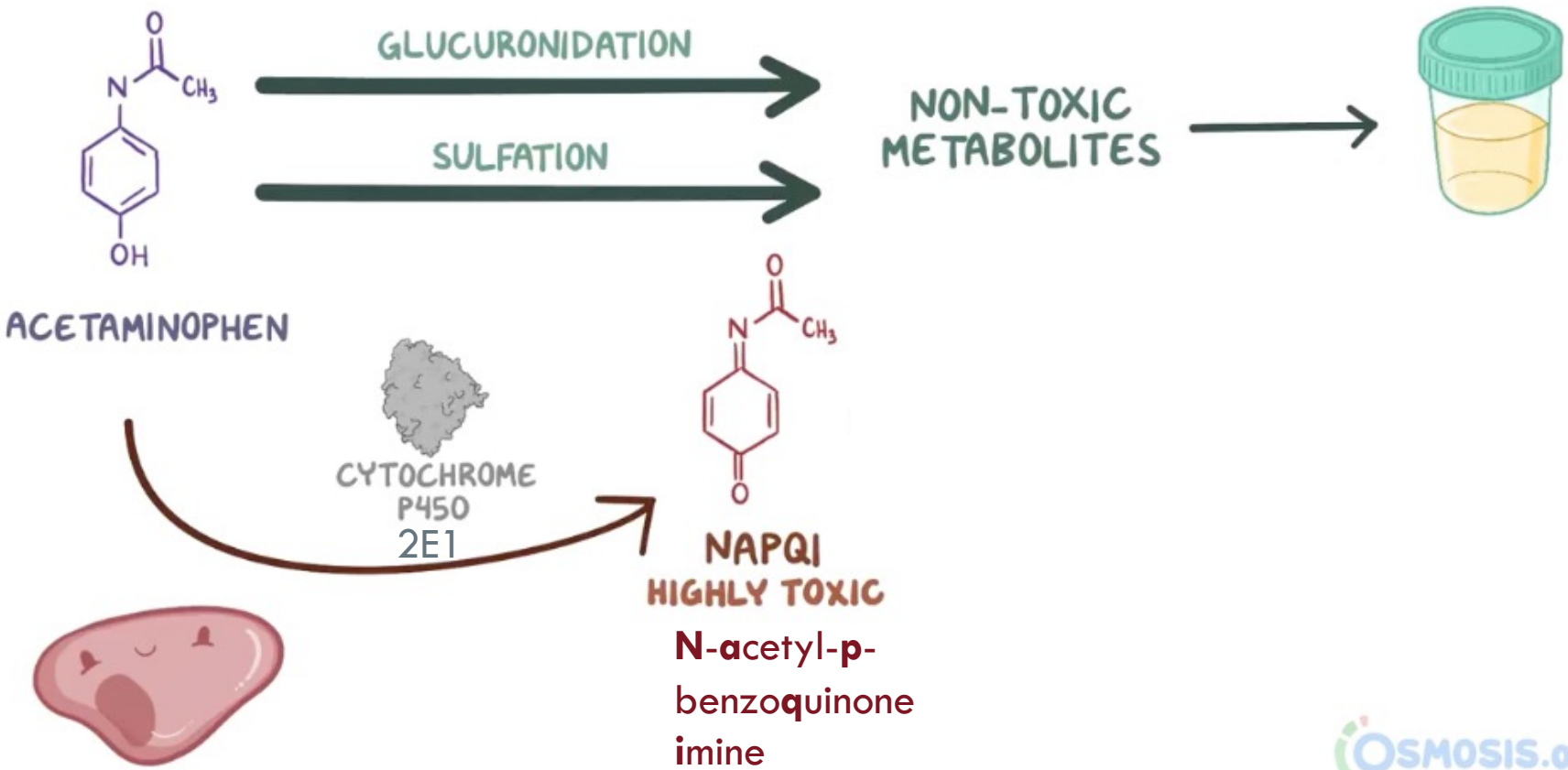
THE CASE OF UR

Acetaminophen is also available over-the-counter in 500 mg tablets. UR confused the strength of the acetaminophen they were using and accidentally took more than the adult recommended daily dose. Which toxic metabolite is likely being produced in excess in UR? Which antidote would UR be administered if they had an unintentional overdose of acetaminophen?

ACETAMINOPHEN METABOLISM

Phase II Reactions

Phase I Reaction

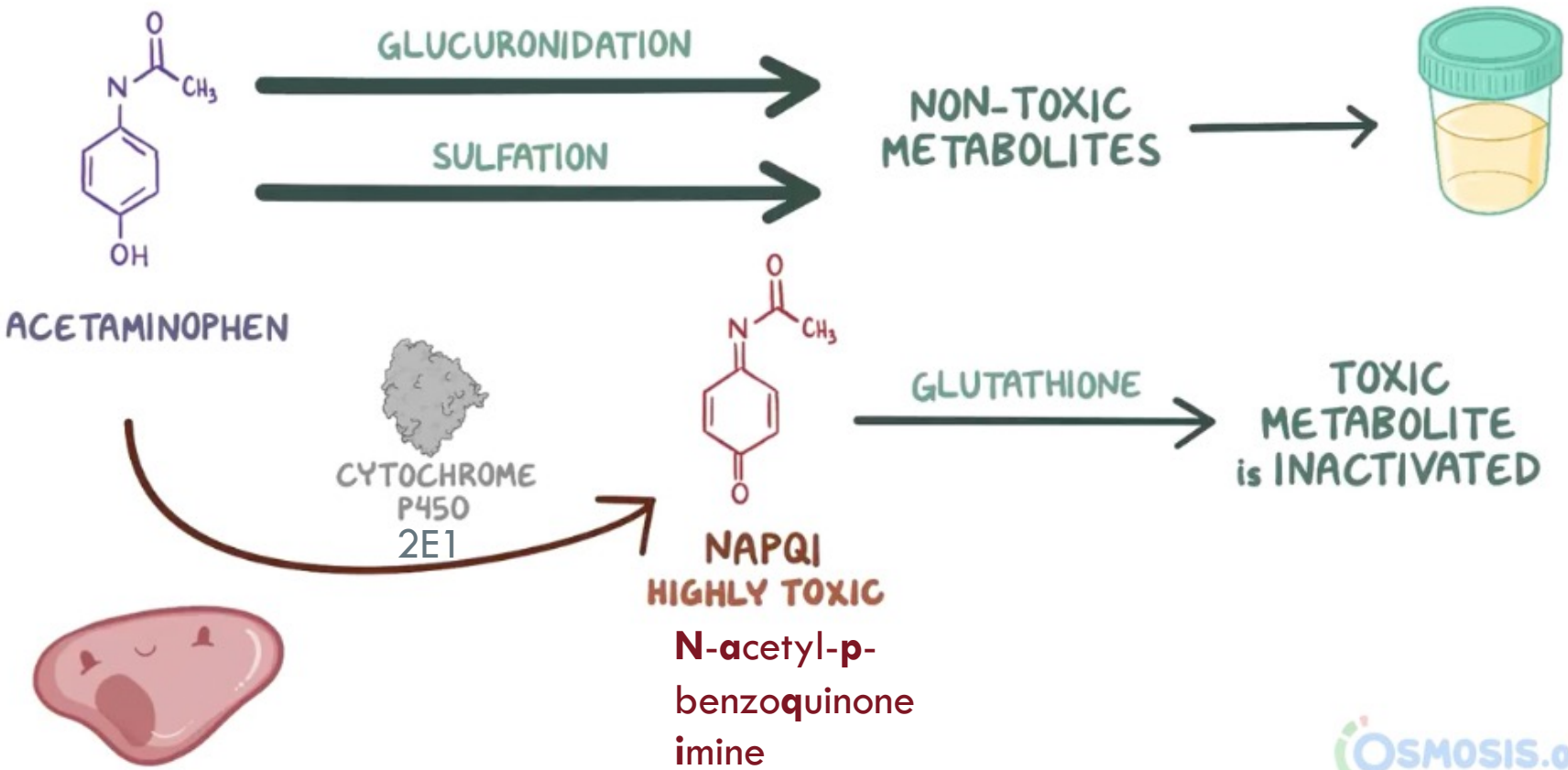


N-**a**cetyl-**p**-benzo**q**uinone **i**mine

ACETAMINOPHEN METABOLISM

Phase II Reactions

Phase I Reaction



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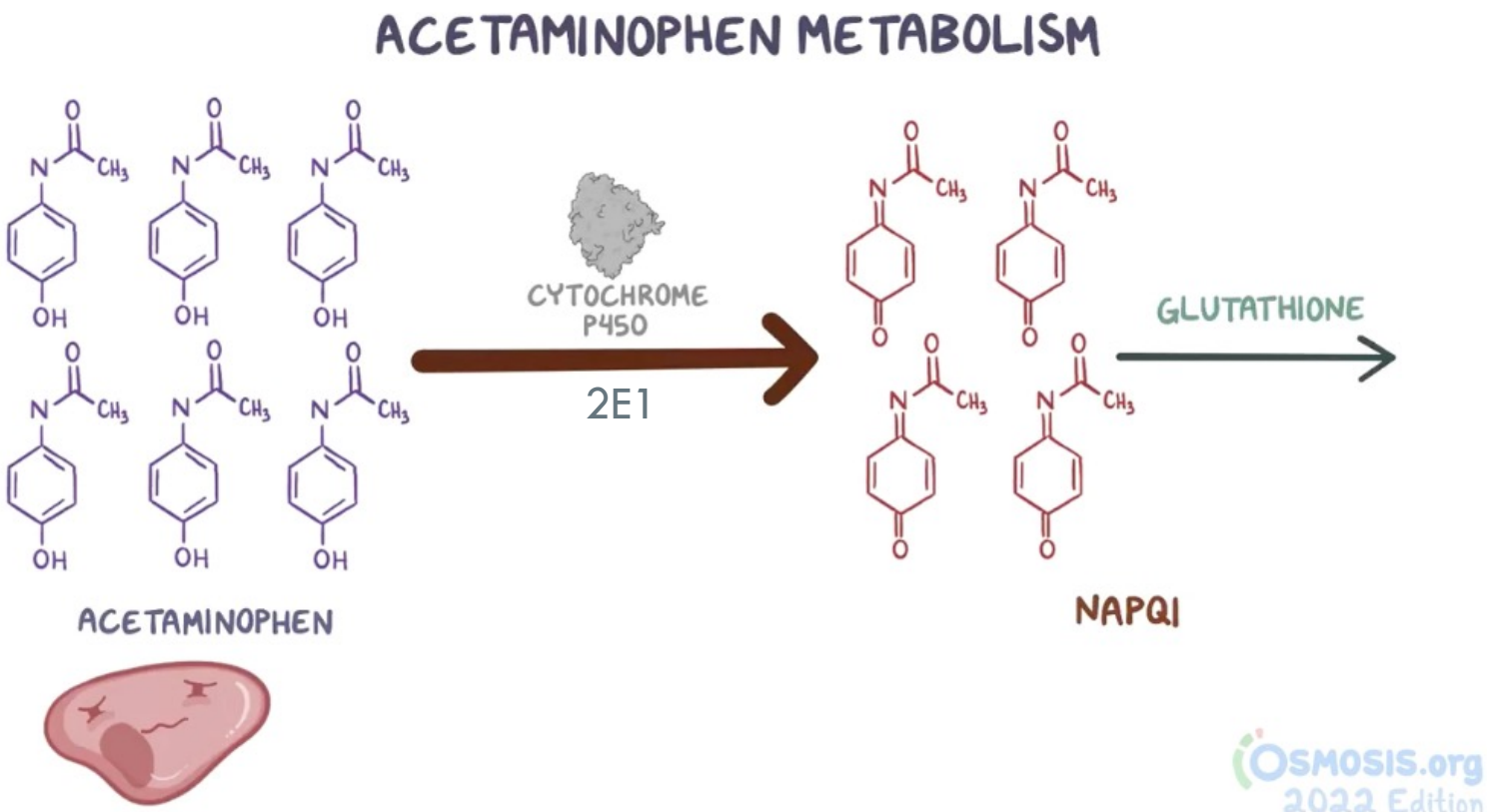
GLUTATHIONE DEPLETION



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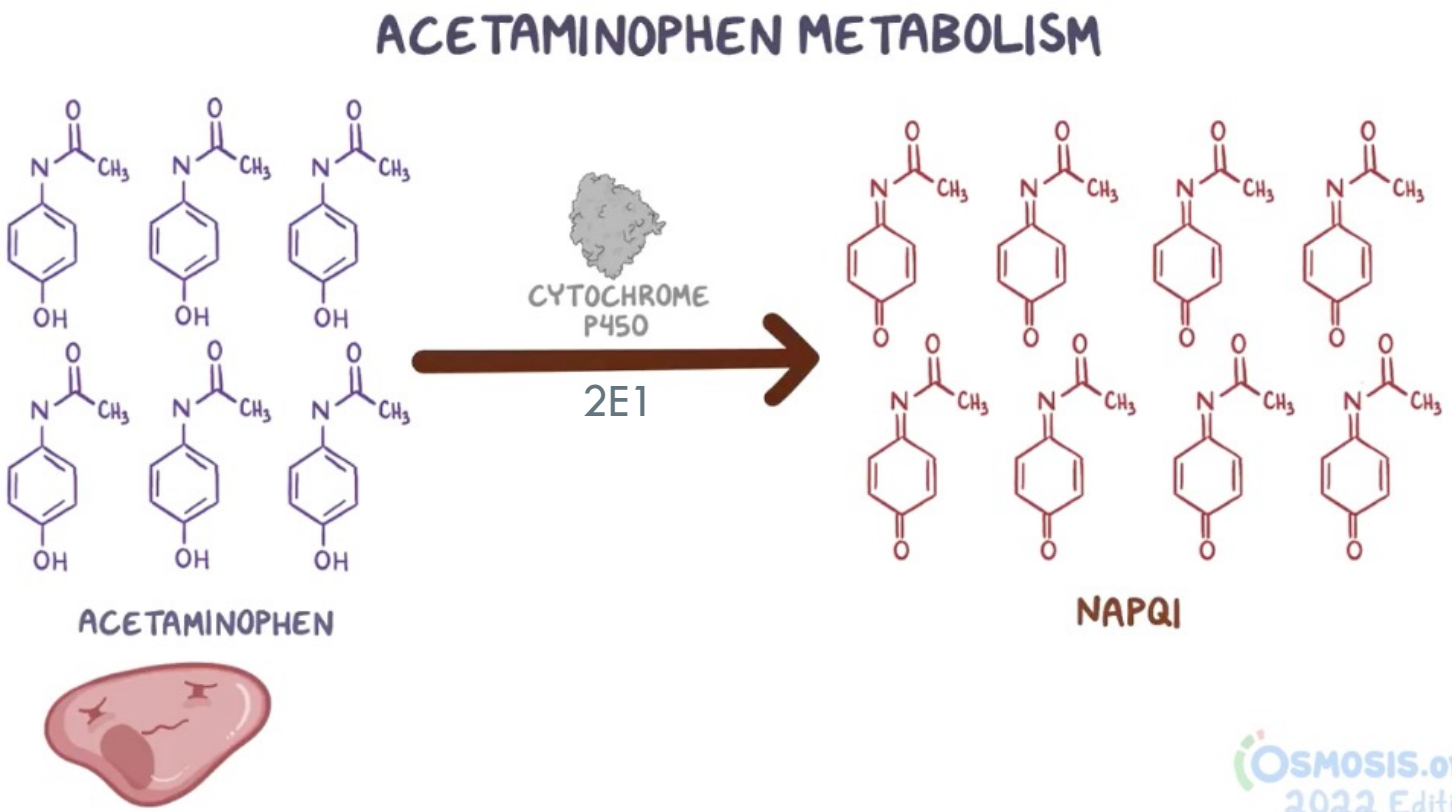

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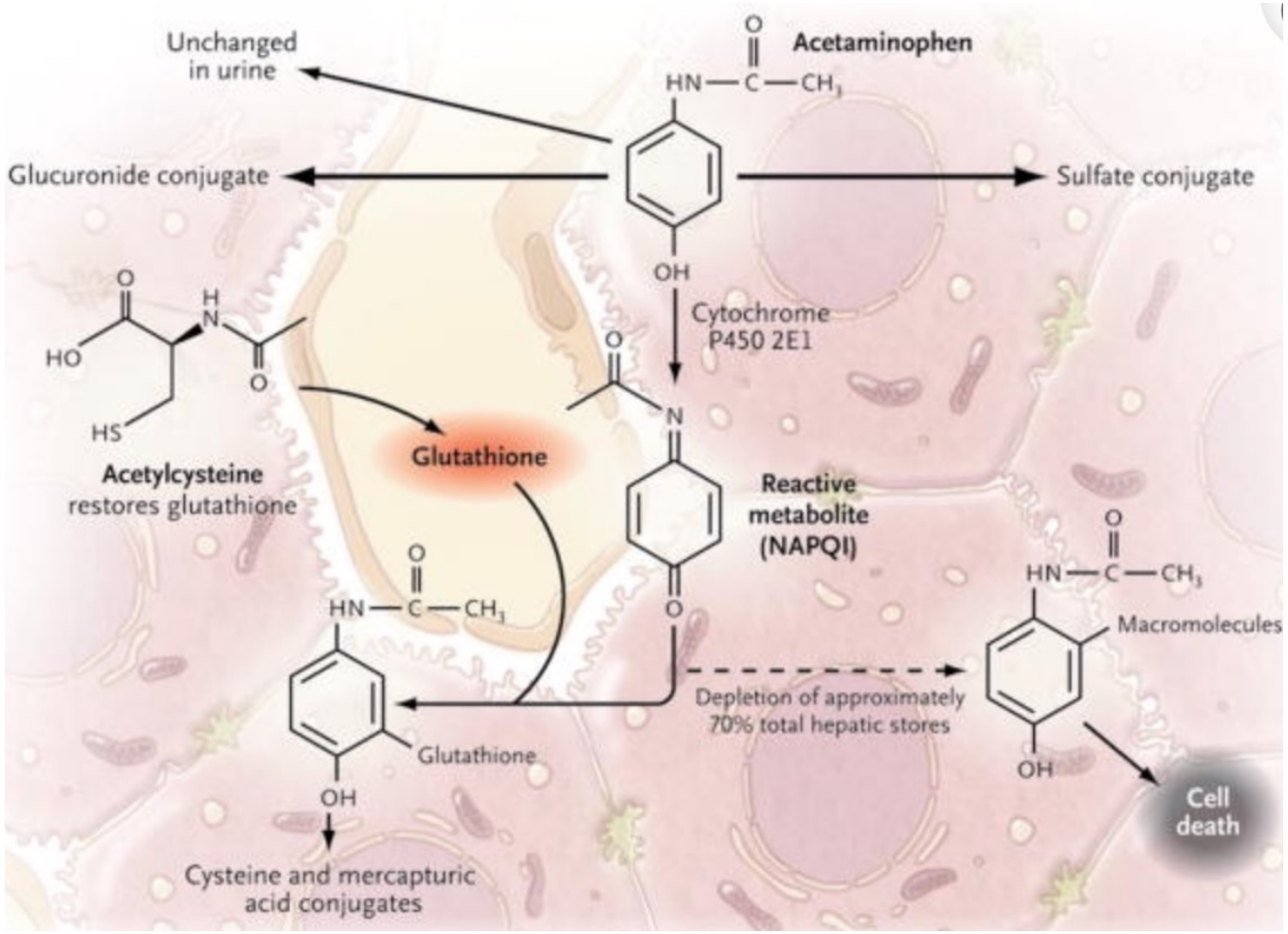

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ACETAMINOPHEN TOXICITY

May occur with supratherapeutic doses

- 15 grams may be fatal
- 4 - 6 grams associated with increased LFTs

May occur with therapeutic doses

- Individuals with decreased glutathione stores (infants, older adults, malnutrition, glutathione synthesis deficiency)

May occur with chronic use of alcohol or some medications

- Increases activity of CYP450 → increased NAPQI

ACETAMINOPHEN TOXICITY

Early Symptoms

Non-specific

Nausea

Vomiting

Dyspepsia

Worsening Symptoms

Jaundice

Coagulopathy

Hepatic encephalopathy

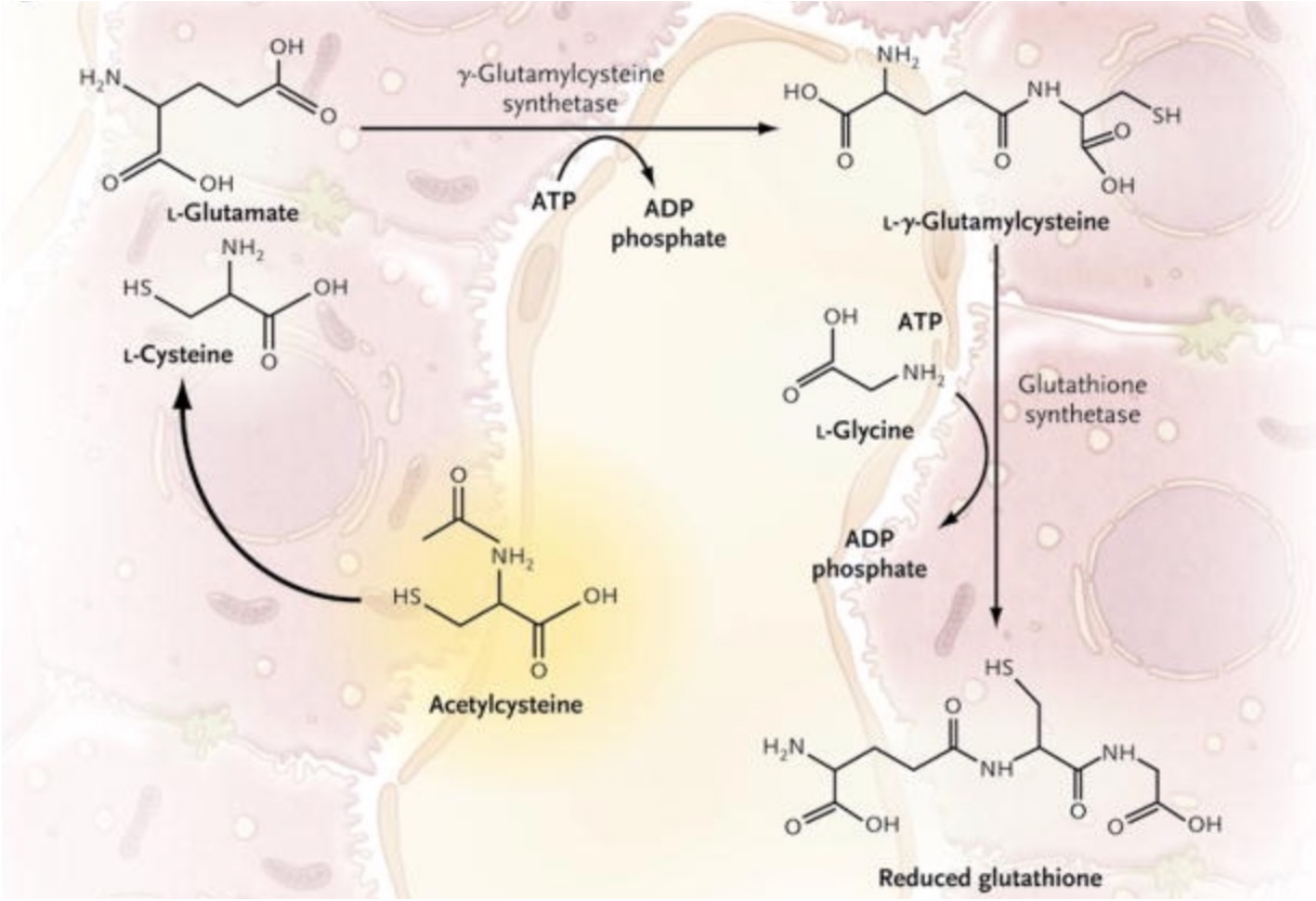
Acute renal failure

ACETAMINOPHEN ANTIDOTAL THERAPY

Administer n-acetylcysteine (NAC)

- Replenishes glutathione stores
- Provides cysteine for glutathione synthesis
- Cysteine is rate-limiting factor in glutathione synthesis

NAPQI inactivated



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GENERAL APPROACH TO TOXICITY

Maintain vital physiologic functions

Reduce or prevent absorption and enhance elimination to minimize the tissue concentration of the poison

- Adsorption
- Whole-bowel irrigation
- Enhancing the elimination of poisons

Combat the toxicological effects of the poison at the effector sites

- Antidotal therapies

SPECIFIC TOXICITY ANTIDOTES

Toxin	Treatment/Antidote
Acetaminophen	N-acetylcysteine
Acetylcholinesterase inhibitors	Atropine > pralidoxime
Antimuscarinic, anticholinergic agents	Physostigmine
Arsenic	Dimercaprol, succimer
Benzodiazepines	Flumazenil
Beta-blockers	Atropine, glucagon, saline
Carbon monoxide	Oxygen
Copper	Penicillamine, trientine

Toxin	Treatment/Antidote
Cyanide	Hydroxycobalamin, nitrites + sodium thiosulfate
Dabigatran	Idarucizumab
Digoxin	Digoxin-specific antibody fragments
Direct factor Xa inhibitors	Andexanet alfa
Heparin	Protamine sulfate
Iron (Fe)	Deferoxamine, deferasirox, deferiprone

SPECIFIC TOXICITY ANTIDOTES

Toxin	Treatment/Antidote
Lead	Calcium disodium EDTA, dimercaprol, succimer, penicillamine
Mercury	Dimercaprol, succimer
Methanol, ethylene glycol (anti-freeze)	Fomepizole, ethanol, dialysis
Methemoglobin	Methylene blue, vitamin C
Methotrexate	Leucovorin
Opioids	Naloxone
Salicylates	Sodium bicarbonate (NaHCO3)

Toxin	Treatment/Antidote
Tricyclic Antidepressants (TCAs)	Sodium bicarbonate (NaHCO3)
Warfarin	Vitamin K

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DRUG INTERACTIONS

DRUG INTERACTIONS

Differences in rate of metabolism of a drug can be due to drug interactions

- Two drugs co-administered and subjected to metabolism by the same enzyme

Drug interactions occur when one drug modifies the actions of another drug

DRUG INTERACTION TERMINOLOGY

Drug Effect	Definition	Example
Additive	The effect of two drugs given together is equal to the sum of the responses to the same doses given separately	Aspirin + acetaminophen ("2 + 2 = 4")
Antagonism	The effect of two drugs given together is less than the sum of the responses to the same doses given separately	Vitamin K given as antidote to warfarin ("2 + 2 < 4")
Synergism	The effect of two drugs given together is greater than the sum of the responses to the same doses given separately	Clopidogrel + aspirin ("2 + 2 > 4")

DRUG INTERACTIONS

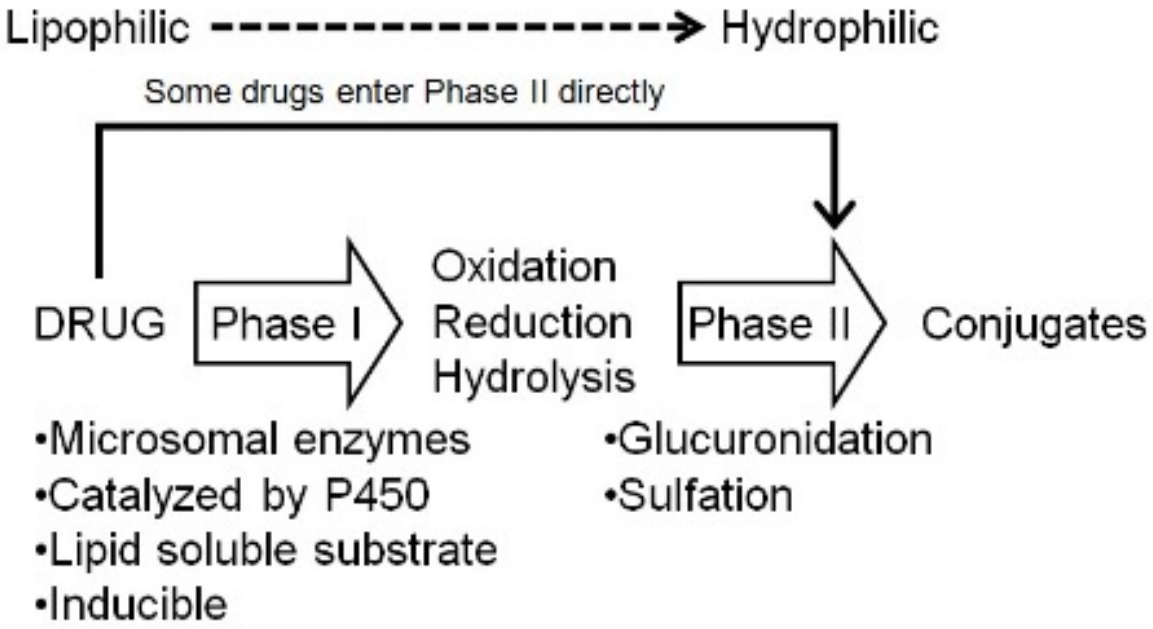
Focus on interactions based on metabolic clearance

Most drug interactions are due to phase I reactions (CYPs)

- Identify the CYP that metabolizes a particular drug

Increased risk

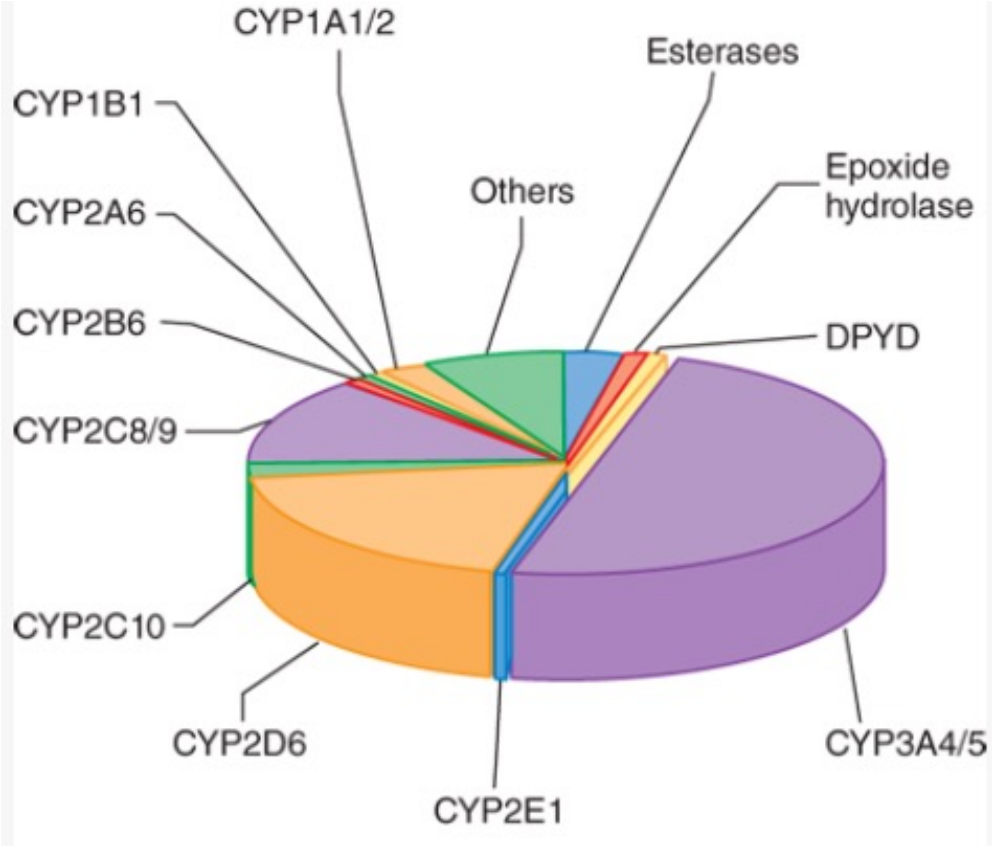
- Individuals using multiple drugs
- Older adults



PHASE I REACTIONS

Fraction of clinically used drugs metabolized by phase I enzymes

Sometimes more than a single enzyme is responsible for metabolism of a single drug



ACTIVE LEARNING

Which two CYP enzymes metabolize the largest proportion of drugs?

DRUG INTERACTION TERMINOLOGY

Substrate	Drug or other substance metabolized by CYP450 enzymes
Inhibitor	Blocks the metabolic activity of CYP450 enzymes
Inducer	Enhances the metabolic activity of CYP450 enzymes

ACTIVE LEARNING

Drug A is a substrate of CYP3A4, Drug B is an inhibitor of CYP3A4, and Drug C is an inducer of CYP3A4.

Compared to Drug A being administered alone, how would you expect the concentration of Drug A to change when administered with Drug B?

ACTIVE LEARNING

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Compared to Drug A being administered alone, how would you expect the concentration of Drug A to change when administered with Drug C?

ACTIVE LEARNING

You have a patient using cyclosporine s/p solid organ transplant. Your patient presents with an infection and you are considering the use of the following antibiotics: azithromycin, clarithromycin, or erythromycin. **If you were only considering the potential for drug interactions,** which antibiotic would be most appropriate for your patient? Defend your answer.

CYP3A4

Enzyme	Substrate	Potent Inhibitors	Potent Inducers
CYP3A4	alprazolam (Xanax) amlodipine (Norvasc atorvastatin (Lipitor) cyclosporine (Sandimmune) diazepam (Valium) estradiol (Estrace) simvastatin (Zocor) sildenafil (Viagra) verapamil (Calan) zolpidem (Ambien)	clarithromycin (Biaxin) diltiazem (Cardizem) erythromycin grapefruit juice itraconazole (Sporanox) ketoconazole (Nizoral) nefazodone (Serzone‡) ritonavir telithromycin (Ketek) verapamil (Calan)	carbamazepine Hypericum perforatum (St. John's wort) phenobarbital phenytoin rifampin

CYP2D6

Enzyme	Substrate	Potent Inhibitors	Potent Inducers
CYP2D6	amitriptyline carvedilol (Coreg) codeine donepezil (Aricept) haloperidol (Haldol) metoprolol (Lopressor) paroxetine risperidone (Risperdal) tramadol (Ultram)	amiodarone (Pacerone) cimetidine (Tagamet) diphenhydramine (Benadryl) fluoxetine (Prozac) paroxetine (Paxil) quinidine ritonavir terbinafine (Lamisil)	Not very susceptible to enzyme induction

PRODRUGS

Compound with negligible, or lower, activity against a specified pharmacological target than one of its major metabolites

Biotransformed

- Esterification of a hydroxyl or amine group
- CYP450 enzymes

Purpose

- Improved bioavailability
- Decreased toxicity
- Delivering drug to specific cells or tissues

PRODRUG EXAMPLE

Loratadine (Claritin)

- Readily absorbed
- Undergoes extensive metabolism to descarboethoxyloratadine (principal pharmacologically active agent)
- CYP3A4 and CYP2D6 primarily responsible

ACTIVE LEARNING

Now consider Drug D, a substrate of CYP3A4. Drug D is prodrug that is metabolized to its active form. How would you expect the therapeutic effect of Drug D to be impacted if it were given with carbamazepine, a potent CYP3A4 inducer?

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ANY QUESTIONS?